PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 July 2000 (20.07.00)	
International application No. PCT/GB99/03635	**Applicant's or agent's file reference** N75394B JCI
International filing date (day/month/year) 03 November 1999 (03.11.99)	**Priority date** (day/month/year) 04 November 1998 (04.11.98)
Applicant LALVANI, Ajit et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 June 2000 (05.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Carlos Naranjo
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

IRVINE, Jonquil, Claire
J. A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX
ROYAUME-UNI

Date of mailing (day/month/year) 27 April 2000 (27.04.00)	
Applicant's or agent's file reference N75394B JCI	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/03635	**International filing date** (day/month/year) 03 November 1999 (03.11.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

ISIS INNOVATION LIMITED
2 South Parks Road
Oxford OX1 3UB
United Kingdom

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

ISIS INNOVATION LIMITED
Ewert House
Ewert Place
Summertown
Oxford OX2 7BZ
United Kingdom

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer S. Cruz Telephone No.: (41-22) 338.83.38

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are cited:

   D1: WO 98 23960 A
   D2: BRANDT, L. ET AL.: J. IMMUNOL., vol. 1996, no. 157, 1996, pages 3527-3533
   D3: HARBOE, M. ET AL.: INFECT. IMMUN., vol. 66, no. 2, February 1998 , pages 717-723
   D4: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 90
   D5: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 108
   D6: ULRICHS, T. ET AL.: EUR. J. IMMUNOL., vol. 28, no. 12, December 1998, pages 3949-3958
   D7: ELHAY, M.J. ET AL.: INFECT. IMMUN., vol. 66, no. 7, July 1998, pages 3454-3456

2. The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D4, D5 and D6 cited in the international search report could become relevant.

3. For the purpose of the present report, the unclear claim 6 has been interpreted as referring to an analogue which can bind a T cell receptor which recognizes the **equivalent** (or corresponding) substituted peptide, see page 9, lines 3-5 of the description and present claims 7-9.

4. The present application is based on the surprising finding that the peptide "ES1" represented by SEQ ID NO:1 and corresponding to amino acids 1-15 of the ESAT-6 protein of Mycobacterium tuberculosis is suitable to detect nearly 60% of human TB patients. This finding could not be expected from any of the relevant prior art documents D1, D2, D3 and D7.

Example 3 of D1 identified T-cells im M. tuberculosis patients reactive with the peptides ES12 (amino acids 69-76) and ES13 (amino acids 82-90), but not with the peptide ES8 (amino acids 10-18).
D2 discloses that the peptide ES1 contains a T-cell epitope recognized by T-cells taken from M. tuberculosis-infected mice. When faced with the problem of providing peptides suitable for detection of infection in **humans**, a person skilled in the art would not have extrapolated the data of D2 obtained from mice to the diagnosis of humans, because it is known that mice have different MHC molecules than humans and are thus expected to recognize different epitopes. This is also apparent from the finding that the peptide ES2 was not identified as an epitope-containing fragment of the ESAT-6 protein by the mouse studies of D2, while the present application found this peptide to detect 40% of TB patients. Furthermore, there are no indications or suggestions in D2 to use the disclosed peptides in diagnosis.

Therefore, novelty and inventive step of the claimed subject-matter is acknowledged.

Re Item VIII

Certain observations on the international application

5. Claims 6-9 and 24 relating to analogues are formulated as dependent claims, although these claims are broader in scope than the claims on which they (formally) depend. These claims are therefore unclear and confusing, contrary to Article 6 PCT.

Claim 19 is somewhat unclear since it is drafted in the second/further medical use format although it does not actually refer to a medical or diagnostic application.

CLAIMS:

1. A method of determining infection in a human by, or exposure of a human to, a mycobacterium which expresses ESAT-6 comprising:

(i) contacting a population of T cells from said human with the peptide represented by SEQ ID NO:1 and, optionally, one or more further peptides represented by SEQ. ID. NOs. 2 to 11 and

(ii) determining *in vitro* whether the T cells of said T cell population recognise said peptide(s).

2. Use of the peptide represented by SEQ ID NO:1 and, optionally, one or more further peptides represented by SEQ. ID. NOs: 2 to 11, for the preparation of a means for use in determining in a human infection by, or exposure to, a mycobacterium which expresses ESAT-6, said method comprising determining whether T cells of said human recognise said peptide(s).

3. A method or use according to claim 1 or claim 2 wherein a peptide panel is employed consisting of, in addition to the peptide represented by SEQ. ID NO:1, one or more peptides selected from the peptides represented by SEQ. ID. NOs. 2 to 11.

4. A method or use according to claim 3 wherein at least the peptides represented by SEQ. ID. NOs. 1 to 8 are employed.

5. A method or use according to claim 4 wherein one or more further peptides are employed selected from the peptides represented by SEQ. ID. NOs. 9, 10 and 11.

6. A method or use according to any one of claims 1 to 5 wherein any of said peptides is substituted by an analogue which can bind a T cell receptor which recognises the peptide.

7. A method or use as claimed in any one of claims 1 to 5 wherein any of said peptides is

substituted by a peptide analogue which is at least 70% homologous, preferably at least 80% homologous, more preferably at least 90% homologous, to the entire corresponding substituted peptide and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

8. A method or use as claimed in claims 1 to 5 wherein any of said peptides is substituted by a peptide analogue which has one or more deletions at the N–terminus and/or C-terminus and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

9. A method or use as claimed in any one of claims 1 to 5 and 8 wherein any of said peptides is substituted by a peptide analogue which has one or more conservative substitutions compared to the corresponding substituted peptide and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

10. A method or use according to any one of the preceding claims in which the recognition of the peptide(s) by the T cells is determined by determining secretion of a cytokine from the T cells.

11. A method or use according to claim 10 in which IFN-γ secretion from the T cells is determined.

12. A method or use according to claim 11 in which IFN-γ secretion from the T cells is determined by allowing secreted IFN-γ to bind to an immobilised antibody specific to the cytokine and then determining the presence of antibody/cytokine complex.

13 . A method or use according to any one of the preceding claims in which the T cells are freshly isolated *ex vivo* cells from peripheral blood.

14. A method or use according to any one of claims 1 to 12 in which the T cells are pre-cultured *in vitro* with the peptide(s).

15. A method or use according to any one of the preceding claims in which the mycobacterium is *M. tuberculosis* or *M. bovis*.

16. A kit for carrying out a method or use according to any one of the preceding claims comprising a peptide panel as defined in any one of claims 3 to 5, or any one of claims 6 to 9 as dependent on claims 3 to 5, and optionally a means to detect the recognition of a peptide by the T cells.

17. A kit according to claim 16 which includes an antibody to IFN-γ.

18. A kit according to claim 17 wherein said antibody is immobilised on a solid support and which optionally also includes a means to detect any antibody/IFN-γ complex.

19. Use of one or more polynucleotides capable of expressing in human cells peptide or peptides in accordance with any one of claims 1 to 9 for the preparation of a means for use in determining in a human infection by, or exposure to, a mycobacterium which expresses ESAT-6, said method comprising determining whether T cells of said human recognise said peptide(s).

20. A kit for carrying out a use according to claim 19 comprising one or more polynucleotides capable of expressing in human cells a peptide panel as defined in any one of claims 3 to 5, or claims 6 to 9 as dependent on claims 3 to 5.

21. A pharmaceutical composition comprising a peptide panel as defined in any one of claims 3 to 5, or claims 6 to 9 as dependent on claims 3 to 5, or one or more polynucleotides capable of expressing the peptides of said panel in human cells together with a pharmaceutically acceptable carrier or diluent.

22. A method of diagnosing infection in a human by, or exposure of a human to, a

mycobacterium which expresses ESAT-6 comprising:

(i) contacting a population of T cells from said human with a panel of peptides represented by SEQ. ID. Nos. 1 to 8, wherein said T cells are freshly isolated *ex vivo* cells from peripheral blood, and

(ii) determining *in vitro* whether T cells of said T cell population show a recognition response to said peptides by determining IFN-γ secretion from the T cells.

23. A method as claimed in claim 22 wherein said panel is expanded to additionally include one or more further peptides selected from the peptides of SEQ. ID. NOs. 9 to 11.

24. A method as claimed in claim 22 or claim 23 wherein one or more of said peptides is substituted by an analogue as defined in any one of claims 6 to 9.

25. A method or use as claimed in any one of claims 3 to 9 and 22 to 24 wherein said peptides are pooled.

26. A method as claimed in any one of claims 1 to 9 and 22 to 25 wherein presence of a mycobacterium which expresses ESAT-6 is determined in a suspected healthy contact who has been exposed to said mycobacterium.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/35 C07K7/08 C07K16/12 C12Q1/68 G01N33/68
G01N33/569 G01N33/53 A61K38/10 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12Q A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 23960 A (ISIS INNOVATION ;LALVANI AJIT (GB); BROOKES ROGER HAMILTON (GB)) 4 June 1998 (1998-06-04) cited in the application page 12 -page 13 ---	1-22
X	BRANDT, L. ET AL.: "Key Epitopes on the ESAT-6 Antigen Recognized in Mice During the Recall of Protective Immunity to Mycobacterium tuberculosis." J. IMMUNOL., vol. 1996, no. 157, 1996, pages 3527-3533, XP002134895 page 3528, column 2, paragraph 3 table 1 --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2000	19/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mata Vicente, T.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HARBOE, M. ET AL.: "B-Cell Epitopes and Quantification of the ESAT-6 Protein of Mycobacterium tuberculosis" INFECT. IMMUN., vol. 66, no. 2, February 1998 (1998-02), pages 717-723, XP002134896 figure 2 page 721, column 2, paragraph 3 ---	17,19, 20,22
P,X	PATHAN, A. ET AL.: "Human T Cell Responses to the Antigen ESAT-6 Characterize a Vacine Candidate and Potential Diagnostic Test for Tuberculosis." IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998 (1998-12), page 90 XP002134897 abstract ---	1-22
P,X	PATHAN, A. ET AL.: "Identification of Conserved, CD8+ Cytotoxic T Cell Epitopes in ESAT-6, a Tuberculosis Vaccine Candidate." IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998 (1998-12), page 108 XP002134898 abstract ---	1-22
P,X	ULRICHS, T. ET AL.: "Differential T cell responses to Mycobacterium tuberculosis ESAT6 in tuberculosis patients and healthy donors." EUR. J. IMMUNOL., vol. 28, no. 12, December 1998 (1998-12), pages 3949-3958, XP000891644 page 3952, paragraph 2 page 3955, column 2, paragraph 1 ---	1-22
A	ELHAY, M.J. ET AL.: "Delayed-Type Hypersensitivity Responses to ESAT-6 and MPT64 from Mycobacterium tuberculosis in the Guinea Pig." INFECT. IMMUN., vol. 66, no. 7, July 1998 (1998-07), pages 3454-3456, XP002134900 abstract page 3454, column 2, paragraph 2 -page 3455, column 1, paragraph 1 ---	1-22
A	WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995 (1995-01-12) page 57, line 4 - line 19 -----	1-22

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/GB 99/ 03635

Box I Observations where certain claims were found unsearchable (Continuati n of Item 1 of first sheet)

This International Search Report has not been establisned in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although as far as prophylactic methods are concerned, claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are oependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (3, 14) - complete, (1, 2, 4, 7-13, 15-22) - partially

A peptide with SEQ ID NO:1 or an analog thereof, a polynucleotide encoding it and uses thereof in diagnostics, in pharmaceutical compositions and to produce antibodies.

2. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:2.

3. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

Idem as in subject 1, but referred to SEQ ID NO:3.

4. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:4.

5. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

Idem as in subject 1, but referred to SEQ ID NO:5.

6. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:6.

7. Claims: (1, 2, 5, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:7.

8. Claims: (1, 2, 5, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:8.

9. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:9.

10. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:10.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:11.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07K 14/35, 7/08, 16/12, C12Q 1/68, G01N 33/68, 33/569, 33/53, A61K 38/10, 31/70

A2

(11) International Publication Number: WO 00/26248

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(21) International Application Number: PCT/GB99/03635

(22) International Filing Date: 3 November 1999 (03.11.99)

(30) Priority Data:

9824213.4	4 November 1998 (04.11.98)	GB
60/107,004	4 November 1998 (04.11.98)	US

(71) Applicant *(for all designated States except US)*: ISIS INNOVATION LIMITED [GB/GB]; 2 South Parks Road, Oxford OX1 3UB (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LALVANI, Ajit [GB/GB]; Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU (GB). PATHAN, Ansar, Ahmed [PK/GB]; Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU (GB).

(74) Agents: IRVINE, Jonquil, Claire et al.; J. A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: TUBERCULOSIS DIAGNOSTIC TEST

(57) Abstract

A method of diagnosing in a host infection by or exposure to a mycobacterium which expresses ESAT-6 comprising (i) contacting a population of T cells from the host with one or more peptides or analogues selected from the peptides represented by SEQ ID NO:1 to 11 and analogues thereof which can bind a T cell receptor which recognises any of the said peptides, and (ii) determining whether the T cells of said T cell population recognise the peptide(s) and/or analogue(s). The method may be performed *in vivo*. Peptides and a kit which enable the method to be carried out are provided.

FOR THE PURPOSES OF INFORMATION ONLY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

IRVINE, Jonquil C.
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5LX
GRANDE BRETAGNE

J. A. KEMP & Co
REC'D - 8 FEB 2001
Action by.....

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.02.01
Applicant's or agent's file reference: N75394B JCI	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03635	03/11/1999	04/11/1998

Applicant: ISIS INNOVATION LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hingel, W Tel.+49 89 2399-8717

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N75394B JCI		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03635	03/11/1999	04/11/1998
International Patent Classification (IPC) or national classification and IPC		
C07K14/35		
Applicant		
ISIS INNOVATION LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/06/2000	05.02.01
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Giebeler, K Telephone No. +49 89 2399 8546

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03635

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03635

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-29 as originally filed

Claims, No.:

1-26 as received on 22/01/2001 with letter of 19/01/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB99/03635

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are cited:

   D1: WO 98 23960 A
   D2: BRANDT, L. ET AL.: J. IMMUNOL., vol. 1996, no. 157, 1996, pages 3527-3533
   D3: HARBOE, M. ET AL.: INFECT. IMMUN., vol. 66, no. 2, February 1998 , pages 717-723
   D4: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 90
   D5: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 108
   D6: ULRICHS, T. ET AL.: EUR. J. IMMUNOL., vol. 28, no. 12, December 1998, pages 3949-3958
   D7: ELHAY, M.J. ET AL.: INFECT. IMMUN., vol. 66, no. 7, July 1998, pages 3454-3456

2. The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D4, D5 and D6 cited in the international search report could become relevant.

3. For the purpose of the present report, the unclear claim 6 has been interpreted as referring to an analogue which can bind a T cell receptor which recognizes the **equivalent** (or corresponding) substituted peptide, see page 9, lines 3-5 of the description and present claims 7-9.

4. The present application is based on the surprising finding that the peptide "ES1" represented by SEQ ID NO:1 and corresponding to amino acids 1-15 of the ESAT-6 protein of Mycobacterium tuberculosis is suitable to detect nearly 60% of human TB patients. This finding could not be expected from any of the relevant prior art documents D1, D2, D3 and D7.

Example 3 of D1 identified T-cells im M. tuberculosis patients reactive with the peptides ES12 (amino acids 69-76) and ES13 (amino acids 82-90), but not with the peptide ES8 (amino acids 10-18).
D2 discloses that the peptide ES1 contains a T-cell epitope recognized by T-cells taken from M. tuberculosis-infected mice. When faced with the problem of providing peptides suitable for detection of infection in **humans**, a person skilled in the art would not have extrapolated the data of D2 obtained from mice to the diagnosis of humans, because it is known that mice have different MHC molecules than humans and are thus expected to recognize different epitopes. This is also apparent from the finding that the peptide ES2 was not identified as an epitope-containing fragment of the ESAT-6 protein by the mouse studies of D2, while the present application found this peptide to detect 40% of TB patients. Furthermore, there are no indications or suggestions in D2 to use the disclosed peptides in diagnosis.

Therefore, novelty and inventive step of the claimed subject-matter is acknowledged.

Re Item VIII

Certain observations on the international application

5. Claims 6-9 and 24 relating to analogues are formulated as dependent claims, although these claims are broader in scope than the claims on which they (formally) depend. These claims are therefore unclear and confusing, contrary to Article 6 PCT.

Claim 19 is somewhat unclear since it is drafted in the second/further medical use format although it does not actually refer to a medical or diagnostic application.

CLAIMS

1. A method of diagnosing infection in a host, or exposure of a host, to a mycobacterium which expresses ESAT-6 comprising
(i) contacting a population of T cells from the host with one or more peptides or analogues selected from the peptides represented by SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, and analogues thereof which can bind a T cell receptor which recognises any of the said peptides, but not (a) SEQ ID NO:3 or 5 or an analogue thereof alone, nor (b) a combination of peptides and/or analogues selected from SEQ ID NO:3 and 5 and analogues thereof; and
(ii) determining *in vitro* whether the T cells of said T cell population recognise the peptide(s) and/or analogue(s).

2. Use of one or more peptides or analogues selected from the peptides represented by SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, and analogues thereof which can bind a T cell receptor which recognises any of the said peptides, but not (a) SEQ ID NO:3 or 5 or an analogue thereof alone, nor (b) a combination of peptides and/or analogues selected from SEQ ID NO:3 and 5 and analogues thereof; for the preparation of a diagnostic means for use in diagnosing in a host infection by or exposure to a mycobacterium which expresses ESAT-6, said method comprising determining whether T cells of the host recognise the peptide(s) and/or analogue(s).

3. A method or use according to claim 1 or claim 2 wherein at least the peptide represented by SEQ ID NO:1 or an analogue thereof is used.

4. A method or use according to claim 1 or claim 2 wherein at least the peptides represented by SEQ ID NO:1, 2, 3, 4, 5 and 6, or instead of any of these peptides their analogues, are contacted with the T cells.

5. A method or use according to any one of the preceding claims wherein at least a peptide represented by SEQ ID NO: 7 and/or 8, or an analogue thereof

is used.

6. A method or use according to any one of the preceding claims wherein at least a peptide represented by SEQ ID NO: 9 and/or 10 and/or 11, or an analogue thereof is used.

7. A method or use according to any one of the preceding claims in which the recognition of the peptide by the T cells is determined by detecting the secretion of a cytokine from the T cells.

8. A method or use according to claim 7 in which the cytokine is IFN-γ.

9. A method or use according to claim 7 or claim 8 in which the cytokine is detected by allowing the cytokine to bind to an immobilised antibody specific to the cytokine and then detecting the presence of the antibody/cytokine complex.

10. A method or use according to any one of the preceding claims in which the T cells are freshly isolated *ex vivo* cells.

11. A method or use according to any one of claims 1 to 9 in which the T cells are pre-cultured *in vitro* with peptide.

12. A method or use according to any one of the preceding claims in which the mycobacterium is *M.tuberculosis* or *M. bovis*.

13. A kit for carrying out a method or use according to any one of the preceding claims comprising one or more peptides or analogues as defined in claim 1 and optionally a means to detect the recognition of the peptide by the T cell.

14. A kit according to claim 13 which has at least the peptide represented by SEQ

ID NO:1 or an analogue thereof.

15. A kit according to claim 13 or claim 14 wherein the means to detect recognition comprises an antibody to IFN-γ.

16. A kit according to claim 15 wherein the antibody is immobilised on a solid support and optionally also a means to detect the antibody/IFN-γ complex.

17. A peptide with the sequence of SEQ ID NO:1, 2, 4, 6, 7, 8, 9, 10 or 11 or an analogue thereof.

18. A diagnostic product or panel comprising one or more peptides or analogues selected from the peptides represented by SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 and analogues thereof which can bind a T cell receptor which recognises any of the said peptides, but not (a) SEQ ID NO:3 or 5 or an analogue thereof alone, nor (b) a combination of peptides selected from SEQ ID NO:3 and 5 and analogues thereof.

19. A polynucleotide which is capable of expressing one or more of the peptides or analogues as defined in claim 1, 3, 4, 5, 6 or 17 for use in *in vivo* diagnosis in a host infection by or exposure to a mycobacterium which expresses ESAT-6.

20. A polynucleotide capable of expression to provide a peptide or analogue as defined in claim 17.

21. A pharmaceutical composition comprising a peptide, product or panel, or polynucleotide as defined in any one of claims 17 to 19; and a pharmaceutically acceptable carrier or diluent.

22. Use of a peptide or analogue as defined in claim 17 to produce an antibody specific to the peptide.

CLAIMS:

1. A method of determining infection in a human by, or exposure of a human to, a mycobacterium which expresses ESAT-6 comprising:

(i) contacting a population of T cells from said human with the peptide represented by SEQ ID NO:1 and, optionally, one or more further peptides represented by SEQ. ID. NOs. 2 to 11 and

(ii) determining *in vitro* whether the T cells of said T cell population recognise said peptide(s).

2. Use of the peptide represented by SEQ ID NO:1 and, optionally, one or more further peptides represented by SEQ. ID. NOs: 2 to 11, for the preparation of a means for use in determining in a human infection by, or exposure to, a mycobacterium which expresses ESAT-6, said method comprising determining whether T cells of said human recognise said peptide(s).

3. A method or use according to claim 1 or claim 2 wherein a peptide panel is employed consisting of, in addition to the peptide represented by SEQ. ID NO:1, one or more peptides selected from the peptides represented by SEQ. ID. NOs. 2 to 11.

4. A method or use according to claim 3 wherein at least the peptides represented by SEQ. ID. NOs. 1 to 8 are employed.

5. A method or use according to claim 4 wherein one or more further peptides are employed selected from the peptides represented by SEQ. ID. NOs. 9, 10 and 11.

6. A method or use according to any one of claims 1 to 5 wherein any of said peptides is substituted by an analogue which can bind a T cell receptor which recognises the peptide.

7. A method or use as claimed in any one of claims 1 to 5 wherein any of said peptides is

substituted by a peptide analogue which is at least 70% homologous, preferably at least 80% homologous, more preferably at least 90% homologous, to the entire corresponding substituted peptide and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

8. A method or use as claimed in claims 1 to 5 wherein any of said peptides is substituted by a peptide analogue which has one or more deletions at the N–terminus and/or C-terminus and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

9. A method or use as claimed in any one of claims 1 to 5 and 8 wherein any of said peptides is substituted by a peptide analogue which has one or more conservative substitutions compared to the corresponding substituted peptide and which retains the ability to be recognised by T cells of a T cell population which recognise the corresponding substituted peptide.

10. A method or use according to any one of the preceding claims in which the recognition of the peptide(s) by the T cells is determined by determining secretion of a cytokine from the T cells.

11. A method or use according to claim 10 in which IFN-γ secretion from the T cells is determined.

12. A method or use according to claim 11 in which IFN-γ secretion from the T cells is determined by allowing secreted IFN-γ to bind to an immobilised antibody specific to the cytokine and then determining the presence of antibody/cytokine complex.

13 . A method or use according to any one of the preceding claims in which the T cells are freshly isolated *ex vivo* cells from peripheral blood.

14. A method or use according to any one of claims 1 to 12 in which the T cells are pre-cultured *in vitro* with the peptide(s).

15. A method or use according to any one of the preceding claims in which the mycobacterium is *M. tuberculosis* or *M. bovis*.

16. A kit for carrying out a method or use according to any one of the preceding claims comprising a peptide panel as defined in any one of claims 3 to 5, or any one of claims 6 to 9 as dependent on claims 3 to 5, and optionally a means to detect the recognition of a peptide by the T cells.

17. A kit according to claim 16 which includes an antibody to IFN-γ.

18. A kit according to claim 17 wherein said antibody is immobilised on a solid support and which optionally also includes a means to detect any antibody/IFN-γ complex.

19. Use of one or more polynucleotides capable of expressing in human cells peptide or peptides in accordance with any one of claims 1 to 9 for the preparation of a means for use in determining in a human infection by, or exposure to, a mycobacterium which expresses ESAT-6, said method comprising determining whether T cells of said human recognise said peptide(s).

20. A kit for carrying out a use according to claim 19 comprising one or more polynucleotides capable of expressing in human cells a peptide panel as defined in any one of claims 3 to 5, or claims 6 to 9 as dependent on claims 3 to 5.

21. A pharmaceutical composition comprising a peptide panel as defined in any one of claims 3 to 5, or claims 6 to 9 as dependent on claims 3 to 5, or one or more polynucleotides capable of expressing the peptides of said panel in human cells together with a pharmaceutically acceptable carrier or diluent.

22. A method of diagnosing infection in a human by, or exposure of a human to, a

mycobacterium which expresses ESAT-6 comprising:

(i) contacting a population of T cells from said human with a panel of peptides represented by SEQ. ID. Nos. 1 to 8, wherein said T cells are freshly isolated *ex vivo* cells from peripheral blood, and

(ii) determining *in vitro* whether T cells of said T cell population show a recognition response to said peptides by determining IFN-γ secretion from the T cells.

23. A method as claimed in claim 22 wherein said panel is expanded to additionally include one or more further peptides selected from the peptides of SEQ. ID. NOs. 9 to 11.

24. A method as claimed in claim 22 or claim 23 wherein one or more of said peptides is substituted by an analogue as defined in any one of claims 6 to 9.

25. A method or use as claimed in any one of claims 3 to 9 and 22 to 24 wherein said peptides are pooled.

26. A method as claimed in any one of claims 1 to 9 and 22 to 25 wherein presence of a mycobacterium which expresses ESAT-6 is determined in a suspected healthy contact who has been exposed to said mycobacterium.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N75394B JCI		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03635	03/11/1999	04/11/1998
International Patent Classification (IPC) or national classification and IPC C07K14/35		
Applicant ISIS INNOVATION LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/06/2000	05. 02. 01
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giebeler, K Telephone No. +49 89 2399 8546

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03635

I. Basis of the r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-29	as originally filed				

Claims, No.:

1-26	as received on	22/01/2001	with letter of	19/01/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re It m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are cited:

   D1: WO 98 23960 A
   D2: BRANDT, L. ET AL.: J. IMMUNOL., vol. 1996, no. 157, 1996, pages 3527-3533
   D3: HARBOE, M. ET AL.: INFECT. IMMUN., vol. 66, no. 2, February 1998 , pages 717-723
   D4: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 90
   D5: PATHAN, A. ET AL.: IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998, page 108
   D6: ULRICHS, T. ET AL.: EUR. J. IMMUNOL., vol. 28, no. 12, December 1998, pages 3949-3958
   D7: ELHAY, M.J. ET AL.: INFECT. IMMUN., vol. 66, no. 7, July 1998, pages 3454-3456

2. The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D4, D5 and D6 cited in the international search report could become relevant.

3. For the purpose of the present report, the unclear claim 6 has been interpreted as referring to an analogue which can bind a T cell receptor which recognizes the **equivalent** (or corresponding) substituted peptide, see page 9, lines 3-5 of the description and present claims 7-9.

4. The present application is based on the surprising finding that the peptide "ES1" represented by SEQ ID NO:1 and corresponding to amino acids 1-15 of the ESAT-6 protein of Mycobacterium tuberculosis is suitable to detect nearly 60% of human TB patients. This finding could not be expected from any of the relevant prior art documents D1, D2, D3 and D7.

Example 3 of D1 identified T-cells im M. tuberculosis patients reactive with the peptides ES12 (amino acids 69-76) and ES13 (amino acids 82-90), but not with the peptide ES8 (amino acids 10-18).
D2 discloses that the peptide ES1 contains a T-cell epitope recognized by T-cells taken from M. tuberculosis-infected mice. When faced with the problem of providing peptides suitable for detection of infection in **humans**, a person skilled in the art would not have extrapolated the data of D2 obtained from mice to the diagnosis of humans, because it is known that mice have different MHC molecules than humans and are thus expected to recognize different epitopes. This is also apparent from the finding that the peptide ES2 was not identified as an epitope-containing fragment of the ESAT-6 protein by the mouse studies of D2, while the present application found this peptide to detect 40% of TB patients. Furthermore, there are no indications or suggestions in D2 to use the disclosed peptides in diagnosis.

Therefore, novelty and inventive step of the claimed subject-matter is acknowledged.

Re Item VIII
Certain observations on the international application

5. Claims 6-9 and 24 relating to analogues are formulated as dependent claims, although these claims are broader in scope than the claims on which they (formally) depend. These claims are therefore unclear and confusing, contrary to Article 6 PCT.

Claim 19 is somewhat unclear since it is drafted in the second/further medical use format although it does not actually refer to a medical or diagnostic application.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
J.A. KEMP & CO.
Attn. IRVINE, JONQUIL CLAIRE.
14 South Square
Gray's Inn
London WC1R 5LX
UNITED KINGDOM

Applicant's or agent's file reference N75394B JCI	Date of mailing *(day/month/year)* 19/04/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 99/03635	International filing date *(day/month/year)* 03/11/1999
Applicant ISIS INNOVATION LIMITED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Andria Overbeeke-Siepkes

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
N75394B JCI		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/03635	03/11/1999	04/11/1998
Applicant		
ISIS INNOVATION LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03635

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although as far as prophylactic methods are concerned, claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (3, 14) - complete, (1, 2, 4, 7-13, 15-22) - partially

A peptide with SEQ ID NO:1 or an analog thereof, a polynucleotide encoding it and uses thereof in diagnostics, in pharmaceutical compositions and to produce antibodies.

2. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:2.

3. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

Idem as in subject 1, but referred to SEQ ID NO:3.

4. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:4.

5. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

Idem as in subject 1, but referred to SEQ ID NO:5.

6. Claims: (1, 2, 4, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:6.

7. Claims: (1, 2, 5, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:7.

8. Claims: (1, 2, 5, 7-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:8.

9. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:9.

10. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:10.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:11.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03635

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9823960 A	04-06-1998	AU 5063298 A	22-06-1998
		EP 0941478 A	15-09-1999
WO 9501441 A	12-01-1995	AU 682879 B	23-10-1997
		AU 7068894 A	24-01-1995
		CA 2165949 A	12-01-1995
		EP 0706571 A	17-04-1996
		NZ 267984 A	22-09-1997
		US 5955077 A	21-09-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
N75394B JCI		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/03635	03/11/1999	04/11/1998
Applicant		
ISIS INNOVATION LIMITED et al.		

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   [ ] filed together with the international application in computer readable form.

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   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

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   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03635

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although as far as prophylactic methods are concerned, claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (3, 14) - complete, (1, 2, 4, 7-13, 15-22) - partially

   A peptide with SEQ ID NO:1 or an analog thereof, a polynucleotide encoding it and uses thereof in diagnostics, in pharmaceutical compositions and to produce antibodies.

2. Claims: (1, 2, 4, 7-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:2.

3. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

   Idem as in subject 1, but referred to SEQ ID NO:3.

4. Claims: (1, 2, 4, 7-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:4.

5. Claims: (1, 2, 4, 7-13, 15, 16, 18, 19, 21) - partially

   Idem as in subject 1, but referred to SEQ ID NO:5.

6. Claims: (1, 2, 4, 7-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:6.

7. Claims: (1, 2, 5, 7-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:7.

8. Claims: (1, 2, 5, 7-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:8.

9. Claims: (1, 2, 6-13, 15-22) - partially

   Idem as in subject 1, but referred to SEQ ID NO:9.

10. Claims: (1, 2, 6-13, 15-22) - partially

    Idem as in subject 1, but referred to SEQ ID NO:10.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: (1, 2, 6-13, 15-22) - partially

Idem as in subject 1, but referred to SEQ ID NO:11.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03635

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/35 C07K7/08 C07K16/12 C12Q1/68 G01N33/68
G01N33/569 G01N33/53 A61K38/10 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12Q A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 23960 A (ISIS INNOVATION ;LALVANI AJIT (GB); BROOKES ROGER HAMILTON (GB)) 4 June 1998 (1998-06-04) cited in the application page 12 -page 13 ---	1-22
X	BRANDT, L. ET AL.: "Key Epitopes on the ESAT-6 Antigen Recognized in Mice During the Recall of Protective Immunity to Mycobacterium tuberculosis." J. IMMUNOL., vol. 1996, no. 157, 1996, pages 3527-3533, XP002134895 page 3528, column 2, paragraph 3 table 1 --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2000	19/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mata Vicente, T.

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARBOE, M. ET AL.: "B-Cell Epitopes and Quantification of the ESAT-6 Protein of Mycobacterium tuberculosis" INFECT. IMMUN., vol. 66, no. 2, February 1998 (1998-02), pages 717-723, XP002134896 figure 2 page 721, column 2, paragraph 3 ---	17,19, 20,22
P,X	PATHAN, A. ET AL.: "Human T Cell Responses to the Antigen ESAT-6 Characterize a Vacine Candidate and Potential Diagnostic Test for Tuberculosis." IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998 (1998-12), page 90 XP002134897 abstract ---	1-22
P,X	PATHAN, A. ET AL.: "Identification of Conserved, CD8+ Cytotoxic T Cell Epitopes in ESAT-6, a Tuberculosis Vaccine Candidate." IMMUNOLOGY, vol. 95, no. SUPPL. 1, December 1998 (1998-12), page 108 XP002134898 abstract ---	1-22
P,X	ULRICHS, T. ET AL.: "Differential T cell responses to Mycobacterium tuberculosis ESAT6 in tuberculosis patients and healthy donors." EUR. J. IMMUNOL., vol. 28, no. 12, December 1998 (1998-12), pages 3949-3958, XP000891644 page 3952, paragraph 2 page 3955, column 2, paragraph 1 ---	1-22
A	ELHAY, M.J. ET AL.: "Delayed-Type Hypersensitivity Responses to ESAT-6 and MPT64 from Mycobacterium tuberculosis in the Guinea Pig." INFECT. IMMUN., vol. 66, no. 7, July 1998 (1998-07), pages 3454-3456, XP002134900 abstract page 3454, column 2, paragraph 2 -page 3455, column 1, paragraph 1 ---	1-22
A	WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995 (1995-01-12) page 57, line 4 - line 19 -----	1-22

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